REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1, 2, 6-11, 15-20, 24-29 and 33-49 are in this case. Claims 36-49 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-2, 6-11, 15-20, 24-29 and 33-35 have been rejected. Claims 1, 6, 9, 15, 18, 24, 27 and 33 have now been amended.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 1-2, 6-11, 15-20, 24-29 and 33-35 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claims 1, 9, 18 and 27 have now been amended.

The Examiner states that claims 1-2, 6-11, 15-20, 24-29 and 33-35 are vague and indefinite in that the metes and bounds of the phrase "suppressive conditions" are unclear.

In order to better define the conditions claimed, claims 1, 9, 18 and 27 have now been amended to recite "non-inductive conditions" instead of "suppressive conditions". Since inductive conditions for various inducible promoters which can be utilized by the present invention are detailed in the instant specification (see for example page 36, lines 15-17), non-inductive conditions, which in essence represent the opposite of inductive conditions are readily apparent to the ordinary skilled artisan. For example, a promoter which is induced by a presence of a culture medium component, will be repressed (or not induced) in the absence of such a component, or vice versa.

The Examiner also states that claim 9 is vague and indefinite in that the metes and bounds of "indicative of an interaction between said first polypeptide and said distinct polypeptide" are unclear. The Examiner further points out that since multiple library members are expressed in cells, it is unclear how an interaction between the first polypeptide and a distinct polypeptide can be distinguished given that other interactions are possible within the cell.

Applicant would like to point out an error in the Examiners understanding of the present invention. In embodiments of the present invention in which a library of expressed (bait or prey) polypeptides is used (e.g., claim 9 and 18) each member of such a library is expressed in a specific cell of a plurality of cells. As such, only one interaction between a bait polypeptide and a prey polypeptide is possible. Cells in which such an interaction occurs survive and thus are isolated and the DNA encoding the library protein is rescued and qualified. On the otherhand, cells in which such an interaction does not occur do not survive thus greatly facilitating isolation of interaction-positive cells.

In view of the above presented arguments and claims amendments Applicant believes to have overcome the Examiner's rejections under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, First Paragraph, Rejections

The Examiner has rejected claims 1-2, 6-11, 15-20, 24-29 and 33-35 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, has possession of the claimed invention. The Examiner's rejections are respectfully traversed. Claims 1, 6, 9, 15, 18, 24, 27 and 33 have now been amended.

The examiner points out that no support is found in the specification for the phrase "a Ras activity".

In the interest of expediting prosecution of this case, Applicant has elected to replace the phrase "Ras activity" with the phrase "Ras signaling". Thus, the phrase "lacking Ras activity" has now been changed to "lacking Ras signaling". The instant specification is replete with references to the signaling function of Ras (see, for example, page 8, line 21 to page 9, line 1) and its importance in maintaining yeast viability. In view of the Ras signaling activity descriptions provided by the instant specification and further in view of references to publications which greatly detail the signaling activity of Ras (see, for example, page 8, lines 19-20), Applicant is of the opinion that the phrase "lacking Ras signaling" is abundantly clear to the ordinary skilled artisan.

The New Matter rejection with respect to the phrase "suppressive conditions" is addressed in the arguments to the 112 second paragraph rejections above.

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 112, first paragraph, rejections.

35 U.S.C. § 102(a) Rejections

The Examiner has rejected claims 1, 6-8, 18-19 and 24-26 under 35 U.S.C. § 102(a) as being anticipated by Takemaru and Moon, The Journal of Cell Biology 149(2), April 17, 2000. The Examiner's rejections are respectfully traversed. Claims 1, 6, 18 and 24 have now been amended.

The Examiner points out that Takemaru and Moon teach expression of pRas(61)ΔF-ßcatR8-C which is comprised of the activated c-HaRas mutant and ß-catenin in the cdc-25 yeast strain. Library cDNAs are fused to the v-Src myristoylation sequence targeted to the plasmalemma to identify polypeptides that interact with pRas(61)ΔF-ßcatR8-C as characterized by Ras activity.

Applicant would like to reiterate the advantages of the present invention in light of the fact that it appears as if the Examiner are not aware of the importance of such advantages.

Numerous prior art methods for identifying protein-protein interactions are known in the art. Likewise, several methods which utilize Ras signaling are also known, including the RRS system utilized by Takemaru and Moon.

One limitation inherent to the prior art methods, including the RRS system, is the inability to discount or reduce false positives which result from interaction-independent translocation of Ras to the cell membrane. In order to overcome this limitation, the present inventor devised a method which utilizes a step which substantially reduces false positive results. Such a step, essentially enables activation of the system in the presence or absence of the prey polypeptides and thus enables to identify and discount cells in which Ras membrane translocation occurs in the absence of the prey. Discounting of such cells enable substantial reduction of (false positive) background which would otherwise greatly complicate the identification and isolation of true positive cells in which Ras membrane translocation results from a true interaction between the bait and prey polypeptides.

This important feature of the present invention is neither described nor suggested by Takemaru and Moon. The Examiner mistakenly interprets the replica plating performed by Takemaru and Moon as the equivalent of the selective library protein expression utilized by the present invention. This is clearly not the case; the replica plating performed by Takemaru and Moon is simply used for ensuring efficient expression of the library cDNA as is clearly detailed on page 250, column 2, under the section entitled "RRS screening". It should be noted that Takemaru and Moon do not teach novel methodology beyond that cited by the references of Broder et al. 1998 and Aronheim 1997. Such a replica plating step does not in any way facilitate or enhance selection of transformants in which Ras translocation is dependent on protein-protein interactions. Thus, it is Applicant's strong opinion that Takemaru and Moon do not in any way anticipate or render obvious the presently claimed methods which employ a selective expression step which is effected via use of an inducible (on/off) promoter for the expression of the bait protein and exposure of transformed cells to separate sets of conditions (e.g. bait-inductive/prey-suppressive; bait-suppressive/prey-inductive; bait-inductive/prey-inductive; bait-suppressive/prey-suppressive). Although such selective conditions are effected in the form of replica plating, each grown under a different condition (one with the inducer the other without), please note that such use of replica plating is profoundly different than that practiced by Takemaru and Moon.

In fact, the above referenced sections of the Takemaru and Moon article as well as the abstract section clearly identify the RRS system as the method used by Takemaru and Moon to qualify protein-protein interactions. The Ras recruitment system (RRS) is based on the translocation of a cytoplasmic Ras to the plasma membrane mediated by protein-protein interaction. Such Ras membrane recruitment results in activation of a viability pathway in yeast and a detectable phenotype. Although RRS is similar to the present approach in that Ras membrane recruitment is utilized for identifying protein-protein interactions, The RRS approach suffers from a severe limitation in that fusion of a membrane protein to Ras will result in its membrane translocation independent of protein-protein interaction and a high false positive signal. Evidence to the above comes from the

fact that Takemaru and Moon did not describe or suggest use of a false positive eliminating step in their study.

Further evidence to the fact that Takemaru and Moon did not utilize selective expression of the bait protein (in their case, catenin) can be found on page 251 column 1, line 13 from the bottom, which states "to confirm the specificity of the interaction, the plasmid encoding CBP was recovered and retransformed into the same yeast strain with either an expression plasmid for Ras(61) .... or a negative control plasmid ....." (emphasis added).

Thus, in sharp contrast to the present invention, the teachings of Takemaru and Moon do not describe or suggest a step which utilizes selective expression (utilizing an inducible promoter) of a bait or prey polypeptide which enables distinguishing between cells exhibiting Ras activity which results from expression and thus interaction with the prey polypeptide and a Ras activity which results from interaction-independent mobilization of Ras to the plasmalemma (i.e., false positive).

In view of the above amendments and remarks it is respectfully submitted that claims 1-2, 6-11, 15-20, 24-29 and 33-35 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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